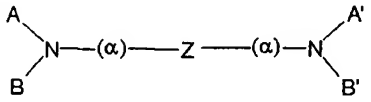
CLAIMS

1/ Precursors of drugs with an anti-malarial action, characterized in that it concerns quaternary bis-ammonium salts and that they correspond to general formula (I)

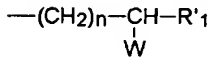



(I)

in which

- A and A' are identical to or different from one another and represent

. either, an $A_1$ and $A'_1$ group respectively, of formula



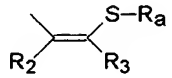

where n is an integer from 2 to 4; $R'_1$ represents a hydrogen atom, a C1 to C5 alkyl radical, optionally substituted by an aryl radical (in particular a phenyl radical), a hydroxy, an alkoxy, in which the alkyl radical comprises from 1 to 5 C, or aryloxy (in particular phenoxy); and W represents a halogen atom chosen from chlorine, bromine or iodine, or a nucleofuge group, such as the tosyl $CH_3-C_6H_4-SO_3$, mesityl $CH_3-SO_3$, $CF_3-SO_3$, $NO_2-C_6H_4-SO_3$ radical,

. or an $A_2$ group which represents a formyl -CHO, or acetyl $-COCH_3$ radical,

- B and B' are identical to or different from one another and represent

. either the $B_1$ and $B'_1$ groups respectively, if A and A' represent $A_1$ and $A'_1$ respectively, $B_1$ and $B'_1$ representing an $R_1$ group which has the same definition as $R'_1$ above, but cannot be a hydrogen atom,

. or the $B_2$ and $B'_2$ groups respectively, if A and A' represent $A_2$, $B_2$ or $B'_2$ being the $R_1$ group as defined above, or a group of formula

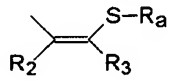



in which -Ra represents an RS- or RCO- group, where R is a linear, branched or cyclic C1 to C6 alkyl radical, optionally substituted by one or more hydroxy or alkoxy (or aryloxy) groups or an amino group and/or a -COOH or COOM group, where M is a C1 to C3 alkyl; a phenyl or benzyl radical, in which the phenyl radical is optionally substituted by at least one C1 to C5 alkyl or alkoxy radical, these being optionally substituted by an amino group, or by a nitrogenous or oxygenous heterocycle, a -COOH or -COOM group; or a $-CH_2$-heterocycle group, with 5 or 6 elements, nitrogenous and/or oxygenous; $R_2$ represents a hydrogen atom, a C1 to C5 alkyl radical, or a $-CH_2$-COO-alkyl (C1 to C5) group; and $R_3$ represents a hydrogen atom, a C1 to C5 alkyl or alkenyl radical, optionally substituted by -OH, a phosphate group, an alkoxy radical, in which the alkyl radical is C1 to C3, or an aryloxy radical; or an alkyl (or aryl), carbonyloxy group; or also $R_2$ and $R_3$ together form a ring with 5 or 6

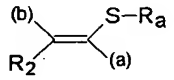
carbon atoms; R and $R_3$ can be linked to form a ring of 5 to 7 atoms (carbon, oxygen, sulphur)

- $\underline{\alpha}$ represents

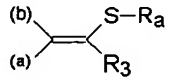
. either a single bond, when $\underline{A}$ and $\underline{A'}$ represent $\underline{A}_1$ and $\underline{A'}_1$: or when $\underline{A}$ and $\underline{A'}$ represent $\underline{A}_2$ , i.e. a -CHO or $-COCH_3$ group, and $\underline{B}_2$ and $\underline{B'}_2$ represent




. or, when $\underline{A}$ and $\underline{A'}$ represent $A_2$ and $\underline{B}_2$ and $\underline{B'}_2$ represent $\underline{R}_1$ , a group of formula



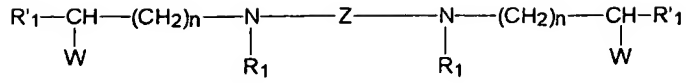

or a group of formula




in which (a) represents a bond towards $\underline{Z}$ and (b) a bond towards the nitrogen atom.

- $\underline{Z}$ represents a C6 to C21 alkyl radical, in particular C13 to C21 optionally with insertion of one or more multiple bonds, and/or one or more O and/or S heteroatoms, and/or one or more aromatic rings, and the pharmaceutically acceptable salts of these compounds.

2/ Precursors according to claim 1, characterized in that it relates to haloalkylamines, corresponding to general formula (II)



(II)

in which $R_1$, $R'_1$, W, n and Z are as defined in claim 1.

3/ Precursors according to claim 1, characterized in that Z represents a C13 to C21 alkyl radical.

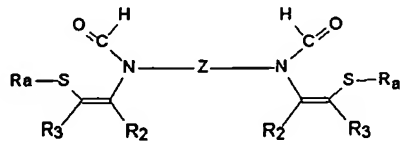
4/ Precursors according to claim 3, characterized in that Z represents a $-(CH_2)_{16}-$ group.

5/ Precursors according to any one of claims 2 to 4, characterized in that $R_1$ is a methyl radical.

6/ Precursors according to any one of claims 2 to 5, characterized in that $R_1$ is a methyl radical and $R'_1$ is either a hydrogen atom, or a methyl radical, and W is a chlorine atom.

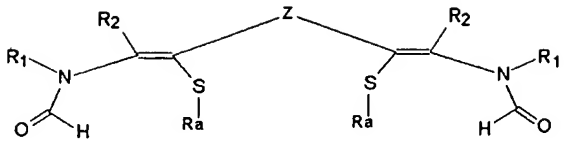
7/ Precursors according to any one of claims 2 to 6, characterized in that they are chosen from N, N'-dimethyl-N,N'-(5-chloropentyl)-1,16-hexadecanediamine hydrochloride, or N, N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride.

8/ Precursors according to claim 1, characterized in that it relates to precursors of thiazolium corresponding to general formula (III).



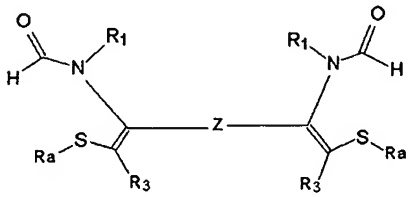
(III)

or to general formula (IV)




(IV)

or to general formula (V)




(V)

in which $\underline{R}_a$, $\underline{R}_1$, $\underline{R}_2$, and $\underline{Z}$ are as defined in claim 1.

9/ Precursors according to claim 8, characterized in that they correspond to formula III in which $\underline{R}_a$ represents an RCO- radical.

10/ Precursors according to claim 9, characterized in that they are chosen from

N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1, 12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-diethylaminomethylphenyl-carboxy)thio-4-methoxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-morpholino-methylphenylcarboxy)-thio-4-methoxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1,16-diaminohexadecane and

N,N'-diformyl-N,N'-di[1(2-oxo-4,5-dihydro-1,3-oxathian-4-ylidene)ethyl]1,12-diaminododecane

11/ Precursors according to claim 8, characterized in that $\underline{R_a}$ represents $\underline{RS-}$.

12/ Precursors according to claim 11, characterized in that they are chosen from

N,N'-diformyl-N,N'-di[1-methyl-2-tetrahydrofurfuryl-methyldithio-4-hydroxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-propyl-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-benzyl-dithio-4-hydroxybut-1-enyl]-1.12 diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-(2-hydroxyethyl)-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3d)

N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-4-methoxybut-1-enyl]-1,12-diaminododecane,

and N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-ethenyl]-1,12-diaminododecane.

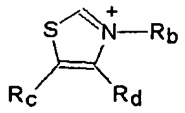
13/ Precursors according to claim 8, characterized in that they correspond to formula IV and are chosen from 2,17-(N,N'-diformyl-N,N'-dimethyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene, 2,17-(N,N'-diformyl-N,N'-

dibenzyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene, ethyl 3,18 (N,N'-diformyl-N,N'-dimethyldiamino-4,17-S-thiobenzoyl-eicosa-3,17-dienedioate (TE12), ethyl 3,18-(N,N'-diformyl-N,N'-dibenzyl)diamino-4,17-S-thiobenzoyl-eicosa-3,17-dienedioate.

14/ Precursors according to claim 8, characterized in that they correspond to formula (V) and are chosen from 2,15-(N,N'-diformyl-N,N'-dimethyl)diamino-1,16-S-thiobenzoyl-hexadeca-1,15-diene.

2,15-(N,N'-diformyl-N,N'-dibenzyl)diamino-1,16-S-thio-benzoyl-hexadeca-1,15-diene.

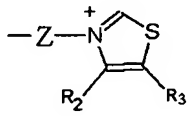
15/ The cyclized derivatives corresponding to the precursors of thiazolium according to any one of claims 8 to 14 corresponding to general formula (VI).



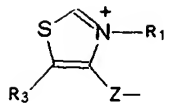
(VI)

in which

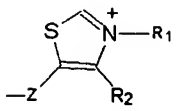
.$\underline{R}_b$ represents $\underline{R}_1$ or $\underline{T}$, $\underline{T}$ representing the group of formula




. $\underline{R}_d$ represents $\underline{R}_2$ or $\underline{P}$, $\underline{P}$ representing the group of formula



$R_c$ represents $R_3$ or U, U representing the group of formula



$R_1$, $R_2$, $R_3$ and Z being as defined in claim 1,

it being understood that $R_b$ = T, if $R_c$ = $R_3$ and $R_d$ = $R_2$; $R_d$ = P, if $R_c$ = $R_3$ and $R_b$ = $R_1$; and $R_c$ = U, if $R_b$ = $R_1$, and $R_d$ = $R_2$.

16/ Process for obtaining precursors of thiazolium of general formula (III) to (IV) according to claim 8, characterized in that it comprises the reaction in basic medium of a thiazole derivative of formula (VI).

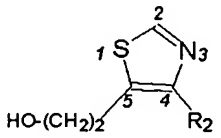
17/ Process according to claim 16, characterized in that in order to obtain the compounds in which $R_a$ = RCO-, a derivative of thiazolium of formula (VI) is reacted with an RCOR' derivative, where R is as defined in claim 1 and R' is a halogen atom, and in order to obtain the compounds in which $R_a$ = RS-, said thiazolium derivatives of formula (VI) are reacted with a thiosulphate derivative $RS_2O_3Na$.

18/ Process according to claim 16 or 17, characterized in that

- in order to obtain the compounds of formula (III) a thiazole derivative suitably substituted with an alkyl dihalide is reacted, under reflux in an organic

solvent, the opening of the thiazolium ring then takes place in basic medium, and by the action either of R-COCl, or of $RS_2O_3N_a$,

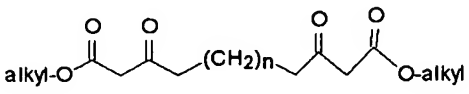
- in order to obtain the compounds of formula IV, which comprise an oxygen in the Z chain, a thiazole derivative of general formula (VII)




(VII)

is reacted with an alkane dihalide, in basic medium, then the addition of $R_1X$, the reaction medium being advantageously taken to reflux in an organic solvent, in particular alcoholic such as ethanol, for a duration sufficient to obtain the quaternization of the nitrogen atom of the thiazole by fixing $R_1$, the opening of the thiazolium ring then being obtained in basic medium, then by the action either of R-COCl, or of $RS_2O_3Na$,

- in order to obtain the compounds of formula (IV) not comprising oxygen in the Z chain, a compound of structure




is firstly synthesized by reacting an alkyl acetoacetate with NaH, followed by alkylation, then the addition of a dihalogenoalkane, the compound obtained